Clinical Neurophysiology 125 (2014) 1639–1646

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Measuring spike strength in patients with continuous spikes and waves during sleep: Comparison of methods for prospective use as a clinical index

M.E. Peltola [a,b,*], V. Sairanen [a,e], E. Gaily [c], S. Vanhatalo [a,d]

[a] Department of Clinical Neurophysiology, Hospital for Children and Adolescents, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland
[b] Department of Clinical Neurophysiology, Turku University Hospital, University of Turku, Turku, Finland
[c] Department of Pediatric Neurology, Hospital for Children and Adolescents, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland
[d] Department of Neurological Sciences, 00014 University of Helsinki, Helsinki, Finland
[e] Department of Physics, 00014 University of Helsinki, Helsinki, Finland

ARTICLE INFO

Article history:
Accepted 4 December 2013
Available online 15 December 2013

Keywords:
CSWS
Electrical status epilepticus during sleep
ESES
Spike amplitude
RMS

HIGHLIGHTS

- Assessment of epileptiform EEG activity in the patients with continuous spikes and waves during sleep (CSWS) needs new objective measures.
- Strength of epileptiform spikes during sleep offers a method complementary to previously used spike index.
- Spatial integration over multiple electrodes during steady NREM sleep renders the measures of spike strength stable enough for clinical use.

ABSTRACT

Objective: To compare methods of estimating spike strength as a potential index in the assessment of continuous spikes and waves during sleep (CSWS).
Methods: Spikes were searched and averaged automatically from pre- and postoperative EEGs of ten patients with CSWS who underwent corpus callosotomy (eight) or resective epilepsy surgery (two). From the most prominent spike, we measured peak amplitude and root mean square (RMS) over ±150 ms window around the peak. In order to compensate for spatiotemporal instability of spikes, the cumulative amplitude and RMS were computed from the highest quartile of electrodes (Ampl-Q and RMS-Q, respectively). The stability of parameters was studied by comparing two ten minute epochs during the first hour of NREM sleep, as well as by analyzing overnight variation of indices in further ten patients with CSWS. The Ampl-Q and RMS-Q were compared between pre- and postoperative recordings.
Results: All four measures, amplitude, RMS, Ampl-Q and RMS-Q, were correlated with each other and highly dependent on NREM/REM-sleep stage and arousals. Expectedly, Ampl-Q and RMS-Q had the greatest intra-individual stability. The amplitude had up to 71% intra-individual variation making it unhelpful for clinical use. Ampl-Q and RMS-Q were comparable in assessing change following surgical treatment.
Conclusions: Computing an integrated RMS over multiple electrodes during steady NREM sleep offers a stable and reliable parameter for evaluating the strength of spikes in CSWS.
Significance: Analyzing spike strength with RMS-Q may offer a clinically useful, supplementary index for EEG monitoring of CSWS where spike index has been of limited value.

1. Introduction

Epilepsy with continuous spikes and waves during sleep (CSWS) is a pediatric epileptic encephalopathy, which is characterized by abundant spike-and-wave discharges during slow wave sleep and eventually seizures (Patry et al., 1971; Tassinari et al., 2000, 2009; Loddenkemper et al., 2011). Electrographic diagnosis of CSWS is commonly defined by estimating the amount of spiking (a.k.a. spike index, SI) in the sleep EEG. Different threshold values from 25% to classical 85% of the NREM sleep have been used (Patry et al., 1971; Tassinari et al., 2000; Inutsuka et al., 2006; Van Hirtum-Das et al., 2006; Scheltens-de Boer, 2009; Saltik et al., 2005; Sánchez

* Corresponding author. Address: Department of Children's Clinical Neurophysiology, Helsinki University Central Hospital, P.O. Box 280, 00029 HUS, Finland. Tel.: +358 9 47180500; fax: +358 9 47180244.
E-mail address: maria.peltola@utu.fi (M.E. Peltola).

1388-2457/$36.00
http://dx.doi.org/10.1016/j.clinph.2013.12.093

Fernández et al., 2012). Treatment of CSWS is challenging (Inutsuka et al., 2006; Aeby et al., 2005; Kramer et al., 2009; Loddenkemper et al., 2009; Liukkonen et al., 2010; Peltola et al., 2011; Veggiotti et al., 2012), and it is further complicated by difficulties in assessing treatment response. Several methodological studies have devised, optimized and tested semiautomatic tools for calculating SI (Chavakula et al., 2009, 2013; Larsson et al., 2009, 2010b; Nonclercq et al., 2012; Peltola et al., 2012; Sánchez Fernández et al., 2012). However, during the course of CSWS, it is uncommon to find a direct correlation between SI and clinical parameters, such as cognitive and behavioral impairments or seizure frequency (Morikawa et al., 1985; Hommet et al., 2000; Sánchez Fernández et al., 2012). Hence, there is an obvious need for developing EEG-based measures that could capture aspects of epileptiform activity other than the temporally cumulating number of spikes measured by SI.

One straightforward and often implicitly estimated EEG feature is the strength, or magnitude, of the epileptic spikes. Using spike strength as a measure gains support from earlier studies reporting how reduction in discharge propagation and/or in the spike amplitude after medical or surgical treatment correlates with a favorable outcome (Larsson et al., 2010a; Peltola et al., 2011). Physiologically, the spike amplitude is considered to express the strength of the epileptic source by combining both the spatial extent and the density of synchronously acting neuronal networks. Such a measure is mechanistically distinct from SI, which reflects the firing activity of neurons involved in the epileptic network irrespective of how strongly and/or widely each individual spike is recruiting the cortical networks. (Cooper et al., 1965; Kobayashi et al., 2005; Tao et al., 2005; Cosandier-Rimélé et al., 2008).

There are several technical paradigms to measure spike strength from multichannel EEG, and better understanding of their characteristics, especially of the stability and sensitivity is essential before introducing the measure into clinical studies. The present study was set out to compare four technical paradigms: Two paradigms measured only the EEG channel with highest spike (peak amplitude and root mean square (RMS)). The other two measures were integrated amplitude and RMS over the highest quartile of channels (Ampl-Q and RMS-Q, respectively), in order to find a balance between spatial specificity of the measure and spatiotemporal variability of the spike propagation.

2. Methods

2.1. Patients

The first part of this study was based on previously published 13 patients with epileptic encephalopathy with CSWS and structural etiology who underwent epilepsy evaluation and surgery during 1991–2005 at the Helsinki University Central Hospital (data set 1) (Peltola et al., 2011). The diagnosis of epileptic encephalopathy with CSWS was based on continuous spike-and-waves occupying at least 85% of NREM sleep in the overnight video-EEG combined with developmental regression, with or without clinical epileptic seizures. These criteria are consistent with the definition of ILAE Task Force on Classification and Terminology (Engel, 2006). The SI was estimated visually by counting the discharge free episodes of minimum duration of ten seconds in the overnight EEG. All patients had either uni- or multifocal bilaterally propagated CSWS preoperatively.

For the present study, we included those ten patients for whom both pre- and postoperative digital EEG recordings were available. Eight of these patients had undergone corpus callosotomy and two focal resections. The EEG and clinical details of the patients are summarized in Supplementary Table S1. Eight patients (numbers 1–5, 7–9 in Supplementary Table S1) had cognitive benefit and over 90% reduction of seizures postoperatively.

In the second part of this study, we analyzed ten EEGs of nine patients with CSWS in whom the whole night recording was available (data set 2). Four of the patients had structural etiology. The recordings were selected randomly from the database of the Epilepsy Unit of the Helsinki University Central Hospital among the patients with suspected or previously diagnosed CSWS between 2006 and 2010. The EEG and clinical details of the patients are summarized in Supplementary Table S2.

2.2. EEG

The EEG data was recorded at 200 Hz with a Telefactor® by using 26–35 scalp electrodes placed according to the International 10–20/10–10 system. The data was viewed and analyzed with the Brain Electrical Source Analysis software version 5.3 (BESA, MEGIS GmbH, Gräfelfing, Germany) (Scherg et al., 2002; Bast et al., 2004). Two epochs of ten minutes during the first hour of NREM sleep were selected randomly from the preoperative EEG (data set 1, Fig. 1A) and one epoch from the postoperative EEG without controlling the stage of NREM sleep. The EEG analysis of the data set 2 was made over the whole night recording.

2.2.1. Spike search

The most prominent spike focus was identified, and the signal was filtered with a 2 Hz forward low-cut filter (6 dB/oct) and 40 Hz zero-phase high-cut filter (24 dB/oct; both filters are built-in functions of BESA® software). A representative typical spike with a fast rise time and high amplitude was chosen for an index spike ("template") for the spatiotemporal pattern search as described earlier (Larsson et al., 2009; Peltola et al., 2012; Bast et al., 2004). Spike search was done using the virtual average montage over all channels with a correlation percentage of 60%. This montage is a standard option in BESA® software, based on estimating the voltage at defined locations of a sphere using spherical spline interpolation from the original EEG signal. Duration of time window for averaging was ± 150 ms around the peak of the largest spike. Baseline was defined from the first 50 ms of the averaging window.

For the data set 1, three different spike averages were computed from the first ten minute epoch of the preoperative EEG data: two averages containing only half of the spike matches, either even or odd spikes, and an average of all spike matches. Only one spike average which included all spike matches was computed from the second ten minute epoch of the preoperative data and from the postoperative data.

For the data set 2, we examined the temporal variation of spike metrics from time series computed by averaging consecutive spikes using a sliding window over the whole night sleep. Akin to the analysis of dataset 1, each individual spike magnitude was first calculated from the ± 150 ms window around the peak of the largest spike. In order to further assess the stability of measures, we computed time courses of averages using different numbers of consecutive spikes (n = 1, 5, 9, 49, and 499).

The average spike epochs were viewed in a virtual Laplacian montage of 27 electrodes (built in function in BESA® software) and exported as ASCII files into Excel 2010® for further analysis.

2.3. Measures of spike strength

We employed four measures of spike strength, two based on single channel, and two based on the combination of channels that together accounted for the highest quartile of spike strength. The latter measures, Ampl-Q and RMS-Q, were introduced to find compensation to the commonly observed spatiotemporal variation of spikes on amplitude related parameters.

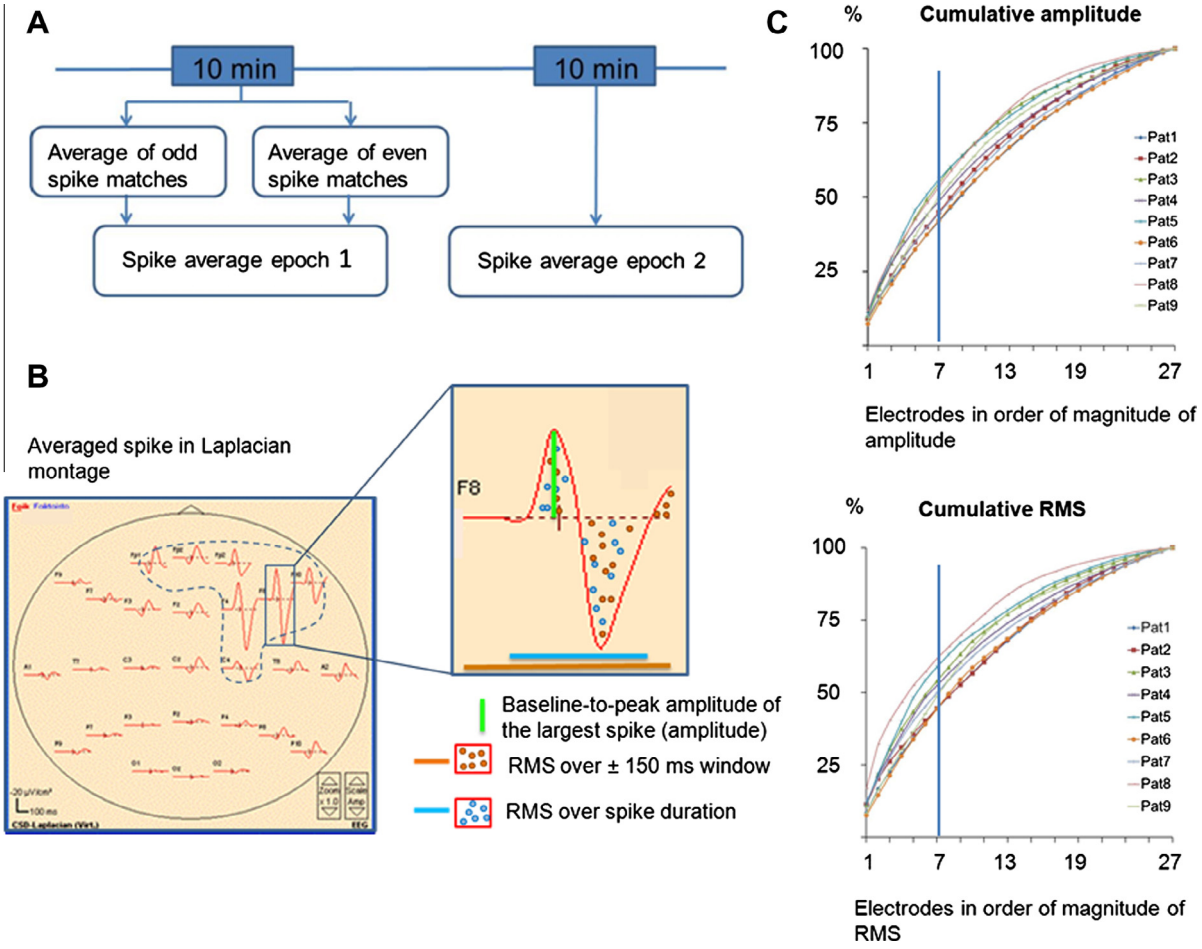

Fig. 1. (A) The study design. (B) The parameters analyzed from the averaged spikes in our study. Quartile measures (Ampl-Q and RMS-Q) were computed from the highest quartile of channels (circled with a dashed line in the top view of head). (C) These graphs demonstrate how the cumulative proportion of amplitude (upper graph) and RMS (lower graph) of the global amplitude increase when more electrodes are added to the sum. The blue vertical line indicates the proportion of global amplitude/RMS explained by the highest quartile of EEG signals (seven out of 27 electrodes).

2.3.1. Single channel measures

The spike amplitude is usually measured from the peak, which, in the signal space, is sensitive to variations in spike morphology and electrode locations. These challenges may be mitigated by analyzing signal power (RMS) over time epoch, or by combining information from multiple scalp electrodes. We measured the baseline-peak amplitude of spike (uV/cm^2) in the Laplacian montage and calculated the RMS (uV/cm^2) over the time period ± 150 ms around the highest peak (Fig. 1B).

2.3.2. Spatially integrated measures

Theoretically, spatiotemporal variation of spikes and/or their propagation patterns may significantly weaken the repeatability of amplitude and RMS measures of a single channel, especially when one aims to follow the parameter between successive EEG recordings. In order to compensate for this uncertainty, we introduced measures that compute the cumulative amplitude and RMS of the highest quartile (i.e. from 7 out of 27 electrodes), called Ampl-Q and RMS-Q, respectively. As demonstrated in Fig. 1C, plotting the cumulative amplitude and RMS against the number of (ranked) channels included does not show any inflection point that would suggest a distinct optimal cutoff. All subjects had a somewhat convex, monotonically rising plots meaning that the choice of highest quartile (as opposed to any other value) is somewhat arbitrary. Yet we chose it because of its methodological simplicity, which is a potential advantage in any prospective clinical applications.

2.4. Comparisons between spike measures

In order to define short time scale 'stability' of amplitude and RMS, we analyzed the variation of these measures by comparing them between the even and odd spikes in the spike search. Further analysis was done from the average of all spikes in each individual. Longer time scale stability of the measures was assessed by comparing two sleep epochs of ten minutes during the first hour of sleep (data set 1). Finally, we computed the temporal variation of measures of spike strength over the night to evaluate their whole night stability (data set 2).

In addition to the analysis over a ± 150 ms window, RMS-Q was calculated over the duration of the largest spike to see if baseline fluctuation or rising slope of slow wave component seen in part of traces has significant effect on RMS-Q over a ± 150 ms window and hence should be eliminated (data set 1). The duration of the spike was defined by observing baseline crossings. The onset of spike was decided visually when one of the following was observed: the change of baseline with signal amplitude < 0.5 $\mu V/cm^2$, the baseline crossing earlier than 75 ms from the beginning of the epoch, and the constantly decreasing or increasing signal up to ± 5.0 $\mu V/cm^2$ without baseline crossing. To assess the utility of 'spike-customized' RMS-Q, it was compared with the RMS-Q over ± 150 ms window.

Finally, the Ampl-Q and the RMS-Q over ± 150 ms window were analyzed from the postoperative data to compare the ability of Ampl-Q and RMS-Q to show a change (either positive or negative)

in spike strength between pre- and postoperative recordings (data set 1). Relative change was calculated as [(preoperative value−postoperative value)/preoperative value]∗100.

2.5. Statistics

The statistical analysis was performed with the IBM SPSS® software version 20.0 (IBM Corp., Armonk, NY, USA). Differences between the groups were evaluated with Wilcoxon Signed Rank test, and considered significant if $p < 0.05$. The pair-wise correlations between parameters were analyzed with Spearman rank correlation test, and considered significant at $p < 0.01$ level (2-tailed). To improve comparability between subjects, we normalized the interquartile range measures by dividing them with the median.

3. Results

3.1. Spike averaging

Stable spike averages were obtained in 19 out of 20 EEGs. One EEG from the data set 1 (Pat. No. 10) was excluded from further analysis because of the complex interference from multiple active foci. The reliability of averaging was shown by a highly significant correlation between the amplitude of even and odd spike averages ($r_{S(7)} = 0.97$, $p < 0.001$) and between the RMS of even and odd spike averages ($r_{S(7)} = 0.98$, $p < 0.001$). Hence, our analysis was carried out after averaging odd and even spike matches together.

3.2. Spike measures

Ampl-Q explained 42–56% of the global sum of spike amplitude, and RMS-Q explained of 44–62% of the global sum of spike RMS (Fig. 1C). Comparison of spike values taken from two consecutive ten minute epochs showed that they were surprisingly stable over this time scale (Supplementary Fig. S1). The RMS was the only parameter that showed statistically significant difference ($Z = -2.67$, $p = 0.008$) between the first and second epoch of ten minutes of preoperative EEG. The median relative difference (absolute value) between the measurements was 4% for the amplitude, 10% for the RMS, 4% for the Ampl-Q and 3% for the RMS-Q (Fig. 2A). However, repeatability, especially that of the amplitude, was notably weak in two patients (Nos. 5 and 7) (Fig. 2B). The single channel spike amplitude varied up to 71%, and the Ampl-Q varied up to 43%. RMS-Q showed the lowest maximal variability of 34%. Despite of the clear differences in intraindividual variabilities, the overall correlation between all measures was expectedly strong ($r_{S(16)} \geqslant 0.96$, $p < 0.001$) (Supplementary Fig. S2).

Next, we reanalyzed the RMS-Q over the duration of the whole spike instead of the fixed ± 150 ms window around the peak to investigate the impact of baseline on the stability of RMS-Q, because the by nature elusive baseline may be a potential confounder. The RMS-Q computed over the spike duration did not differ significantly between the two epochs of ten minutes (Fig. 3A), showing median relative difference (absolute value) of 7%, and the maximal variability of 35%. Moreover, the repeatability of RMS-Q of the ± 150 ms window and of the whole spike duration did not differ significantly (Fig. 3B) and the parameters were strongly correlated ($r_{s(16)} = 0.76$, $p < 0.001$) (Fig. 3C). Consequently, the RMS-Q over the whole spike duration failed to improve the relatively weak repeatability seen in two patients (Nos. 5 and 7) compared to the other patients. A closer inspection of the raw EEG data suggested that the high variability of RMS-Q in these patients was probably caused by the difference of sleep quality between the successive ten minute epochs. During their first ten minute sleep

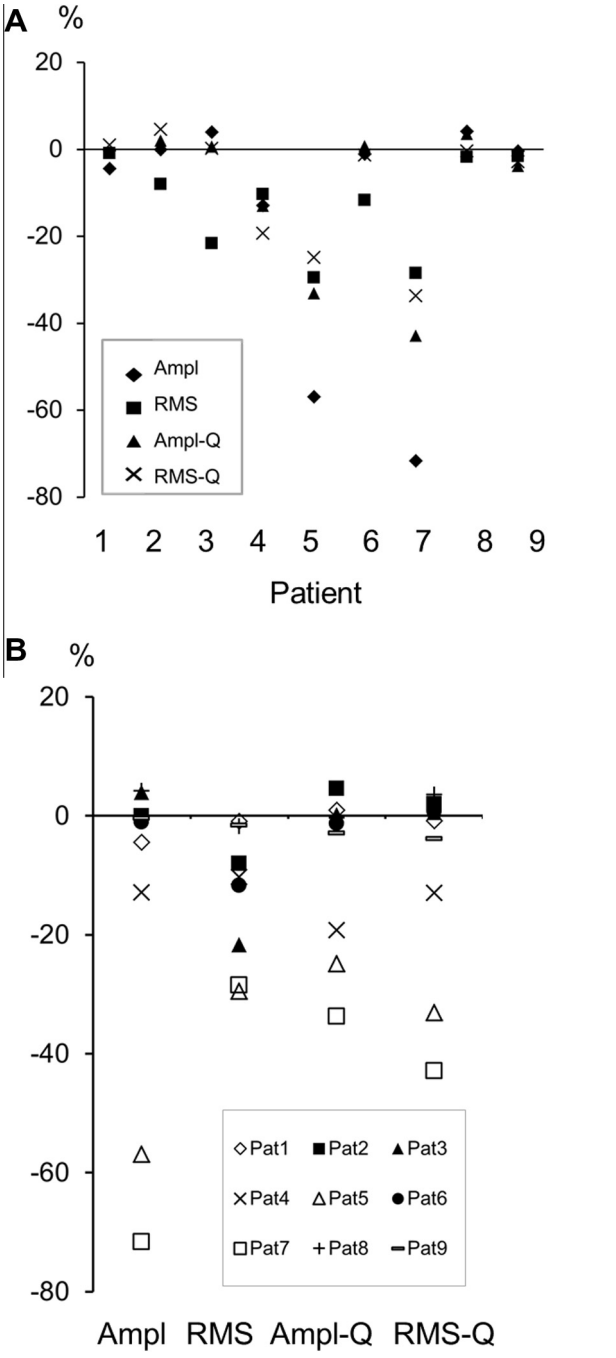

Fig. 2. Short term stability of the measures. (A) The relative difference between two ten minute epochs of EEG during the first hour of NREM sleep in each patient. (B) Grouping of the same results by parameter shows widest distribution with Ampl. Analysis window is ± 150 ms around the peak of the averaged spike containing all spike matches.

epochs, both patients represented multiple short arousals that were associated with a visually clear transient increase in the frequency and decrease in the amplitude of spikes (Supplementary Fig. S3).

Temporal variation of amplitude, RMS, RMS-Q and Ampl-Q was greatest for the time courses of single spikes, and the time courses became expectedly more stable with averaging more consecutive spikes (Supplementary Fig. S4). There was, however, a marked overnight variation. Further inspection of the data indicated that abrupt decreases in spike strength parameters were related to

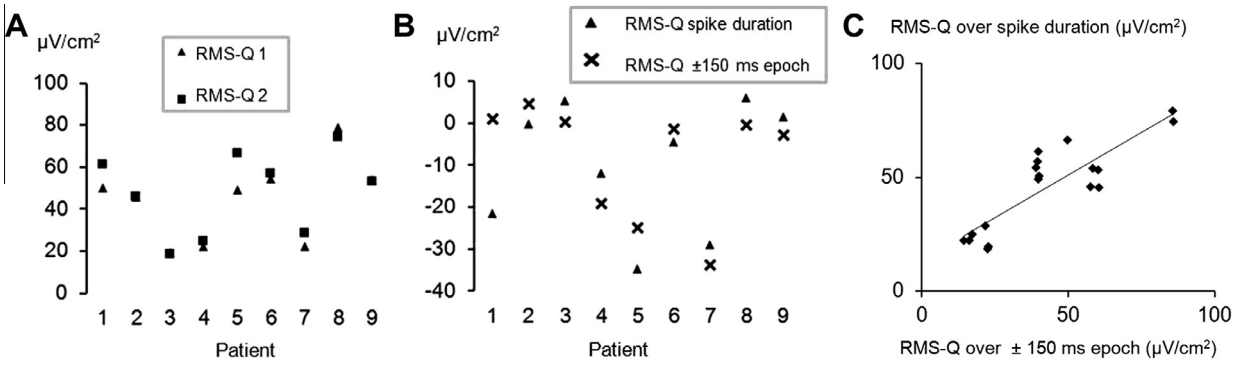

Fig. 3. Comparison of RMS-Q values over time and between methods of computing. (A) Comparability of the RMS-Q over the whole spike duration between two ten minute epochs of EEG. (B) Comparability of RMS-Q computed from the whole spike duration and the ± 150 ms window around the spike peak. (C) Correlation (i.e. stability over time) between the two RMS methods showed by a scatterplot.

arousals and REM-sleep, whereas increases occurred upon transition to NREM sleep (Fig. 4). The clinically most important observations were that (i) Ampl-Q and RMS-Q reached a notably stable plateau during NREM when it was not interrupted by arousals and (ii) no particular NREM period showed constantly better stability than others. The higher likelihood of a NREM sleep in the beginning of the night, however, resulted in generally more stable measures during the first hour of sleep as compared to the whole night averages (Fig. 5). Indeed, this implies that the quality of sleep, or the stability of sleep stage, becomes crucial for a proper, quantitative assessment of spike strength.

3.3. Pre-versus postoperative analysis

In order to analyze the 'sensitivity' of the parameters for changes in spike strength, the most stable parameters Ampl-Q and the RMS-Q were also calculated from the postoperative EEGs and compared with the preoperative measures. We have found earlier (Peltola et al., 2011), that spike amplitudes decrease after successful resection but may either increase or decrease after callosotomy, irrespective of clinical outcome. The Ampl-Q or RMS-Q levels changed in a comparable way after surgery (range 0.5–99% in absolute value, median 79%; Fig. 6).

4. Discussion

Our present results show that spike strength can be reliably measured from the sleep EEG of CSWS patients. The spatial integration of the spike strength measures offers the clinically needed stability of the paradigm. Introducing new EEG-based, conceptually simple measures is needed because the clinical utility of the traditional EEG estimate, SI, is often inconclusive or of limited use for monitoring treatment (Morikawa et al., 1985; Hommet et al., 2000; Sánchez Fernández et al., 2012).

The physiological driver for our approach came from the idea that spike amplitudes reflect the size of associated cortical source area (Cooper et al., 1965; Kobayashi et al., 2005; Tao et al., 2005; Cosandier-Rimélé et al., 2008). Hence, it could be a conceptually straightforward measure of the strength of spikes, but its use is methodologically challenged by the spatiotemporal variation in spike morphology.

At the group level, all our measures (amplitude, RMS, Ampl-Q and RMS-Q) showed expected, strong mutual correlations. However, the measures differed clearly from each other in how much they varied within the individual patient over time. We consider this stability a significant property of an index which would be used for prospective clinical evaluation. The clinically often measured single channel amplitudes showed up to 71% intra-individual variability, making it an unhelpful parameter for clinical use. Likewise, our results indicate that using intuitive single limits of change (for example reduction of 50% of the given parameter) as a threshold of considering significance in therapeutic effects is risky (Aeby et al., 2005; Larsson et al., 2010a; Peltola et al., 2011).

The good performance of Ampl-Q and RMS-Q shown in our study is in agreement with our assumption that spatiotemporal variation can be minimized by combining the data from a set of electrodes over a larger scalp area. However, analyzing the power of signal over a time window (e.g. RMS-Q) instead of using maximal peak value (e.g. Ampl-Q) had, as expected, less effect on the stability of spike strength estimates.

The stability of Ampl-Q and RMS-Q over a ten minute epoch was sufficient for being trialed for clinical purposes in most patients. However, as we found in two of our patients, short arousals during sleep tend to be accompanied by transient changes in spike frequency and spike morphology. This implies that the reliability and repeatability of Ampl-Q and RMS-Q estimates can be notably improved by careful selection of the short (e.g. 10 min) epochs with uninterrupted NREM sleep. Such epoch selection is straightforward and easy for all trained EEGers and technicians. The analysis of overnight variability showed that all spike strength measures are strongly affected by sleep stage, and the measures drop immediately with arousals or transitions to REM. However, no particular NREM period showed constantly better stability than others.

Spike averaging over a time window around the spike peak stabilized the baseline but was unable to fully remove the baseline offset of spikes repeated at the frequency of 1–2.5 Hz. However, reanalysis of RMS-Q using spike duration did not lead to any change, implying that the methodologically simpler way of using a fixed, peak centered narrow window can be used in further studies.

The Ampl-Q and RMS-Q were comparable in showing the change between the pre- and postoperative recordings. We focused on comparing the ability of RMS-Q and Ampl-Q parameters to quantitate a change in spike strength after surgery. Our data with postsurgical recordings was good for that purpose, because it was known to exhibit both positive and negative amplitude responses. Our study was not able to study the sensitivity or specificity of Ampl-Q and RMS-Q in assessing clinical treatment response, because as we showed before (Peltola et al., 2011), amplitude response after callosotomy cannot be used alone as an indicator for treatment outcome. Future studies with more typical (i.e. drug treated) CSWS patients will be needed to quantitatively validate these parameters in following clinical treatment response.

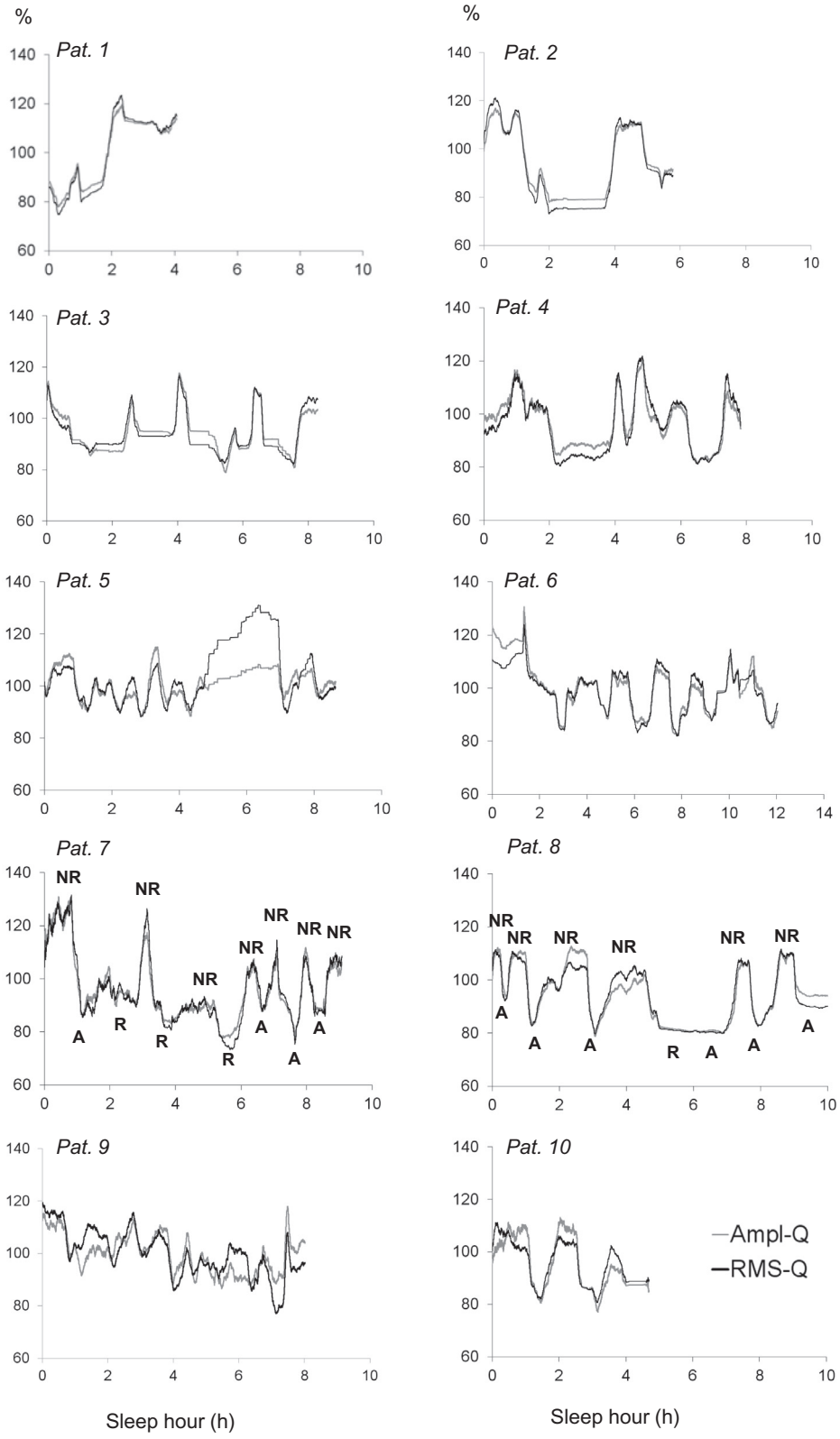

Fig. 4. Relation of spike strength to sleep hour. Transitions between awake, NREM- and REM-sleep were reflected by robust changes in Ampl-Q and RMS-Q (average of 499 spikes). Ampl-Q and RMS-Q time courses are rendered comparable by normalizing them using median of their whole night values. NR = NREM sleep, R = REM sleep, A = awakening.

In conclusion, spatial integration of spike strength measurement to cover the highest quartile yields a stable and sensitive parameter for monitoring of CSWS. Although we found RMS-Q and Ampl-Q to be comparable in our limited dataset, we would like to favor RMS-Q because of its mathematical and physical advantages: The way how RMS is calculated makes it inherently integrated over time and less sensitive to variations that may arise from little changes in spike morphology during sleep or between recordings.

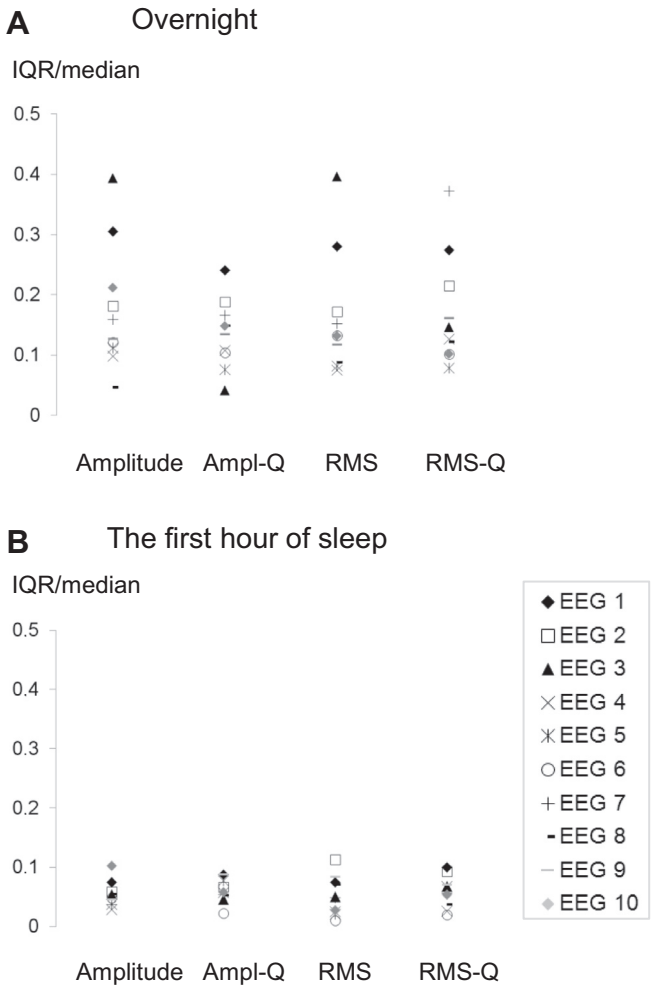

Fig. 5. Comparison of variability of spike strength parameters between (A) the overnight sleep and (B) the first hour of sleep. The measures during the first night of sleep show less variation due to higher probability of steady NREM sleep. IQR = interquartile range.

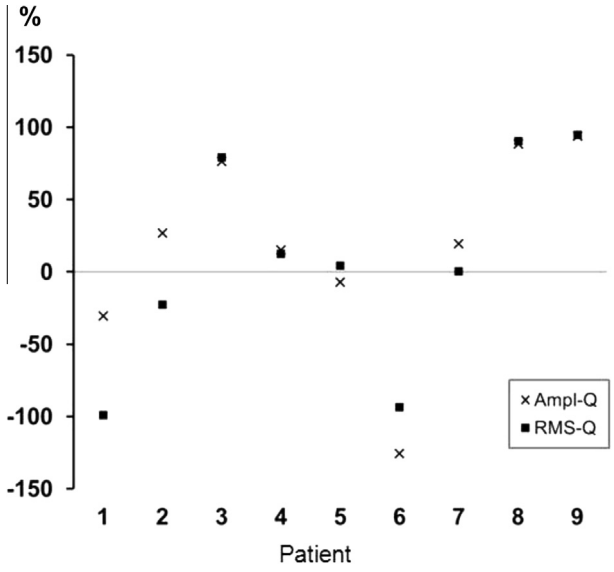

Fig. 6. Relative change of Ampl-Q and RMS-Q between pre- and postoperative EEG.

We used semiautomated spike search, but fully automated spike recognition algorithms have also been found accurate in most CSWS patients (Nonclercq et al., 2012; Chavakula et al., 2013). Indeed, automated spike detection algorithms could be a rational further elaboration of our methodological workup. By reducing operator dependence in the spike search phase, they may hold promise for both higher objectivity and reduced analysis times. As spike strength is thought to reflect different aspects of the pathological network in CSWS compared to spiking activity (SI or the spike frequency), it may add clinical value to EEG monitoring in CSWS. Hence, we propose that in further studies targeted on CSWS, both the strength of spikes, spiking activity and propagation patterns (Peltola et al., 2011) would be used to determine EEG correlates with the clinical states and treatment response.

Disclosure

Eija Gaily has received consulting fees from Eisai and lecture fees from UCB Pharma and Orion Pharma. The other authors have no conflict of interest to disclose.

Acknowledgements

This study was supported by the Finnish National Graduate School of Clinical Investigation, the Finnish Epilepsy Research Foundation and the Finnish Medical Foundation (MEP). SV was supported by the European Community's Seventh Framework Programme European Community FP7-PEOPLE-2009-IOF, grant agreement n°254235.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2013.12.093.

References

Aeby A, Poznanski N, Verheulpen D, Wetzburger C, Van Bogaert P. Levetiracetam efficacy in epileptic syndromes with continuous spikes and waves during slow sleep: experience in 12 cases. Epilepsia 2005;46:1937–42.
Bast T, Oezkan O, Rona S, Stippich C, Seitz A, Rupp A, et al. EEG and MEG source analysis of single and averaged interictal spikes reveals intrinsic epileptogenicity in focal cortical dysplasia. Epilepsia 2004;45:621–31.
Chavakula V, Park EH, Rakhade SN, Rotenberg A, Madsen JR, Loddenkemper T. Measurement of sleep potentiated spiking and electrical status epilepticus in sleep by automated wavelet based EEG analysis. Epilepsia 2009;50(Suppl. 11):36.
Chavakula V, Sánchez Fernández I, Peters JM, Popli G, Bosl W, Rakhade S, et al. Automated quantification of spikes. Epilepsy Behav 2013;26:143–52.
Cooper R, Winter AL, Crow HJ, Walter WG. Comparison of subcortical, cortical and scalp activity using chronically indwelling electrodes in man. Electroencephalogr Clin Neurophysiol 1965;18:217–28.
Cosandier-Rimélé D, Merlet I, Badier JM, Chauvel P, Wendling F. The neuronal sources of EEG: modeling of simultaneous scalp and intracerebral recordings in epilepsy. Neuroimage 2008;42:135–46.
Engel Jr J. ILAE classification of epilepsy syndromes. Epilepsy Res 2006;70(Suppl 1):S5–S10.
Hommet C, Billard C, Barthez MA, Gillet P, Perrier D, Lucas B, et al. Continuous spikes and waves during slow sleep (CSWS): outcome in adulthood. Epileptic Disord 2000;2:107–12.
Inutsuka M, Kobayashi K, Oka M, Hattori J, Ohtsuka Y. Treatment of epilepsy with electrical status epilepticus during slow sleep and its related disorders. Brain Dev 2006;28:281–6.
Kobayashi K, Yoshinaga H, Ohtsuka Y, Gotman J. Dipole modeling of epileptic spikes can be accurate or misleading. Epilepsia 2005;46:397–408.
Kramer U, Sagi L, Goldberg-Stern H, Zelnik N, Nissenkorn A, Ben-Zeev B. Clinical spectrum and medical treatment of children with electrical status epilepticus in sleep (ESES). Epilepsia 2009;50:1517–24.
Larsson PG, Wilson J, Eeg-Olofsson O. A new method for quantification and assessment of epileptiform activity in EEG with special reference to focal nocturnal epileptiform activity. Brain Topogr 2009;22:52–9.

Larsson PG, Eeg-Olofsson O, Michel CM, Seeck M, Lantz G. Decrease in propagation of interictal epileptiform activity after introduction of levetiracetam visualized with electric source imaging. Brain Topogr 2010a;23:269–78.

Larsson PG, Evsiukova T, Brockmeier F, Ramm-Pettersen A, Eeg-Olofsson O. Do sleep-deprived EEG recordings reflect spike index as found in full-night EEG recordings? Epilepsy Behav 2010b;19:348–51.

Liukkonen E, Kantola-Sorsa E, Paetau R, Gaily E, Peltola M, Granstrom ML. Long-term outcome of 32 children with encephalopathy with status epilepticus during sleep, or ESES syndrome. Epilepsia 2010;51:2023–32.

Loddenkemper T, Cosmo G, Kotagal P, Haut J, Klaas P, Gupta A, et al. Epilepsy surgery in children with electrical status epilepticus in sleep. Neurosurgery 2009;64:328–37.

Loddenkemper T, Fernandez IS, Peters JM. Continuous spike and waves during sleep and electrical status epilepticus in sleep. J Clin Neurophysiol 2011;28:154–64.

Morikawa T, Seino M, Osawa T, Yagi K. Five children with continuous spike-wave discharges during sleep. In: Roger J, Dravet C, Bureau M, Dreifuss FE, Wolf P, editors. Epileptic Syndromes in Infancy, Childhood and Adolescence. London: John Libbey Eurotext Ltd; 1985. p. 205–12.

Nonclercq A, Foulon M, Verheulpen D, De Cock C, Buzatu M, Mathys P, et al. Cluster-based spike detection algorithm adapts to interpatient and intrapatient variation in spike morphology. J Neurosci Methods 2012;210:259–65.

Patry G, Lyagoubi S, Tassinari CA. Subclinical "electrical status epilepticus" induced by sleep in children. A clinical and electroencephalographic study of six cases. Arch Neurol 1971;24:242–52.

Peltola ME, Liukkonen E, Granstrom ML, Paetau R, Kantola-Sorsa E, Valanne L, et al. The effect of surgery in encephalopathy with electrical status epilepticus during sleep. Epilepsia 2011;52:602–9.

Peltola ME, Palmu K, Liukkonen E, Gaily E, Vanhatalo S. Semiautomatic quantification of spiking in patients with continuous spikes and waves in sleep: sensitivity to settings and correspondence to visual assessment. Clin Neurophysiol 2012;123:1284–90.

Saltik S, Uluduz D, Cokar O, Demirbilek V, Dervent A. A clinical and EEG study on idiopathic partial epilepsies with evolution into ESES spectrum disorders. Epilepsia 2005;46:524–33.

Sánchez Fernández I, Peters JM, Hadjiloizou S, Prabhu SP, Zarowski M, Stannard KM, et al. Clinical staging and electroencephalographic evolution of continuous spikes and waves during sleep. Epilepsia 2012;53:1185–95.

Scheltens-de Boer M. Guidelines for EEG in encephalopathy related to ESES/CSWS in children. Epilepsia 2009;50(Suppl 7):13–7.

Scherg M, Ille N, Bornfleth H, Berg P. Advanced tools for digital EEG review: virtual source montages, whole-head mapping, correlation, and phase analysis. J Clin Neurophysiol 2002;19:91–112.

Tao JX, Ray A, Hawes-Ebersole S, Ebersole JS. Intracranial EEG substrates of scalp EEG interictal spikes. Epilepsia 2005;46:669–76.

Tassinari CA, Rubboli G, Volpi L, Meletti S, d'Orsi G, Franca M, et al. Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. Clin Neurophysiol 2000;111(Suppl 2):S94–S102.

Tassinari CA, Cantalupo G, Rios-Pohl L, Giustina ED, Rubboli G. Encephalopathy with status epilepticus during slow sleep: "the Penelope syndrome". Epilepsia 2009;50(Suppl 7):4–8.

Van Hirtum-Das M, Licht EA, Koh S, Wu JY, Shields WD, Sankar R. Children with ESES: variability in the syndrome. Epilepsy Res 2006;70(Suppl 1):S248–58.

Veggiotti P, Pera MC, Teutonico F, Brazzo D, Balottin U, Tassinari CA. Therapy of encephalopathy with status epilepticus during sleep (ESES/CSWS syndrome): an update. Epileptic Disord 2012;14:1–11.